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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,522	11/21/2001	Choy-Pik Chiu	097/002	3556

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EXAMINER
NGUYEN, QUANG

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 06/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/990,522	CHIU ET AL.	
	Examin r	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover she t with the correspondence address --

Peri d f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2,3,4,7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' preliminary amendment filed on 4/7/03 in Paper No. 6 has been entered. Applicants elected without traverse the following species: (a) the first cell population has characteristics of mesenchymal stem cells; (b) the first cell population expresses CD90; and (c) the second cell population comprises cardiomyocytes or their lineage-restricted precursors.

Claims 1-20 are pending in the present application, and they are examined on the merits herein.

Priority

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number. At the moment, the priority reference is in the second paragraph of page 2 of the application.

Additionally, the reference to the US provisional patent application 60/252,688 filed November 22, 2000 is not present in the Declaration.

Claim Objections

Claim 20 is objected to because of the following informalities: the phrase "A method for preparing an individual for therapy to reconstitute their cellular function" is not grammatically correct. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to **make and/or** use the invention.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

With respect to the elected invention, the instant claims are drawn to a combination of pharmaceutical compounds comprising: (a) a first cell population that has been differentiated from human pluripotent stem (hPS) cells into a phenotype that

renders a subject to whom it is administered immunotolerant to a second cell population that is differentiated from hPS cells and is MHC compatible with the first cell population, wherein the first cell population has characteristics of mesenchymal stem cells or one that expresses CD90 cell marker and the second cell population comprises cardiomyocytes; a method for preparing the same cell populations for therapeutic use as well as methods for reconstituting cellular function or preparing an individual for therapy to reconstitute their cellular function using the same.

The instant specification describes in general that human ES cells can be differentiated into tolerizing cells by forming embryoid bodies or by direct differentiation in a suitable culture environment with suitable medium, and that relevant markers for mesenchymal stem cells are: CTLA-4, SH2+, SH3+, CD29+, CD44+, CD71+, CD90+, CD106+, CD14-, CD34-, CD45-. Additionally, the present disclosure states that scientists at Geron Corporation have discovered that it is possible to differentiate hPS cells into a highly enriched population comprising cardiomyocytes or cardiomyocyte precursors.

However, the instant specification is not enabled for the presently claimed invention for the following reasons.

(1) The breadth of the claims. The instant claims encompass a combination of pharmaceutical compounds comprising: (a) a first cell population that has been differentiated from human pluripotent stem (hPS) cells into a phenotype that renders any subject to whom it is administered immunotolerant to a second cell population that is differentiated from hPS cells, not necessarily derived from the same hPS cells, and is

MHC compatible with the first cell population, wherein the first cell population has characteristics of mesenchymal stem cells or one that expresses CD90 cell marker and the second cell population comprises cardiomyocytes; a method for preparing the same cell populations for therapeutic use as well as methods for reconstituting cardiomyocyte function or preparing an individual for therapy to reconstitute cardiomyocyte function using the same by administering the first and second cell populationd by any route of delivery into the individual.

(2) The state and unpredictability of the prior art. At the effective filing date of the present application, little is known about tolerance induction and/or cardiac repair or regeneration for human allograft patients using cell populations differentiated from human pluripotent stem cells (Waldmann, Nature Med. 5:1245-1248, 1999; IDS; Sussman, Nature 410:640-641, 2001). Kaufman et al. (PNAS 98:10716-10721, 2001) state "**If** human ES cell-derived HSCs can be used to create hematopoietic chimerism in a patient, that patient should be tolerant to other tissues derived from the same ES cells and would not require any continuous immunosuppressive treatment", and "The clinical promise of human ES cell-base therapies is great; however, because these therapies will be entirely novel, serious concerns about safety and efficacy will need to be addressed before human clinical trials can be initiated" (page 10721, col. 1). Furthermore, in a post-filing art (Nature Med. 8:171-177, 2002; IDS), Fandrich et al. also note that the potential for mouse or human embryonic stem cells or their progenitor cells to survive in an allogenic host environment has not been reported, even in 2002 (page 176, col. 2, second full paragraph).

With respect to the utilization of cardiomyocytes in cardiac muscle repair and/or regeneration, Grounds et al. (J. Histochem. Cytochem. 50:589-610, 2002) state "Although some experiments in animal models report successful engraftment and maturation of embryonic cardiomyocytes in normal and injured hearts ...., other studies show that most of the donor cardiomyocytes (engrafted into mature rat hearts after infarction) retained their embryonic phenotype and did not form junctions with mature heart cells by 4 weeks...Although neonatal donor cells could form junctions with host myocardium, there was massive initial death of donor cells and at later times the grafts were often isolated by scar tissue...This problem is a direct result of the inflammation and scarring after infarction, and it may be that use of cardiomyocyte transplantation therapy could be more effectively developed to address functional improvement in myopathic heart diseases" (page 602, col. 2, first paragraph). Grounds et al. further teach that although it has been shown in tissue culture that human ES cells can also differentiate into cardiomyocytes, human ES cells have a very low efficiency of conversion into cardiomyocytes compared with those of mice (<10% compared with >80% of murine ES cells; a median of 11 days for differentiation compared with 2 days for murine cells), and that the use of embryonic stem cells as a source of cardiomyocytes is an attractive therapeutic possibility that needs to be fully explored (page 604, col. 2 under the section titled "Embryonic stem cells").

(3) The amount of direction or guidance provided. Apart from the general disclosure that human ES cells can be differentiated into tolerizing cells including mesenchymal stem cells, and that it is possible to differentiate hPS cells into a highly

enriched population comprising cardiomyocytes or cardiomyocyte precursors, the instant specification fails to provide any specific guidance including the relevant *in vitro* and *in vivo* examples, for a skilled artisan on how to obtain any effective amount of mesenchemal stem cells derived from hPS cells with the desired property (e.g., rendering the treated individual immunotolerant to the second cell population) and any effective amount of cardiomyocytes differentiated from hPS cells, and their utilization to attain any therapeutic effects contemplated by Applicants (e.g., repair and/or regeneration and/or reconstituting cardiac function in a treated individual or patient). It is unclear under which specific conditions and/or parameters, an effective amount of tolerizing mesenchymal stem cells or tolerizing cells expressing CD90 or cardiomyocytses could be obtained via the differentiation of hPS cells in culture that can be used for obtaining the contemplated therapeutic effects. Particularly, human ES cells are known to be very inefficient to differentiate into cardiomyocytes even in 2002 (Grounds et al.; Cited above). There is no evidence of record indicating that any of the cell populations differentiated from hPS cells could be survived in an allogenic host environment in a sufficient time period to yield the contemplated therapeutic effects. Fandrich et al. note that the potential for mouse or human embryonic stem cells or their progenitor cells to survive in an allogenic host environment has not been reported, even in 2002, let alone at the effective filing date of the present application (page 176, col. 2, second full paragraph). Moreover, in a related study Bachar-Lustig et al. (Blood 94:3212-3221, 1999; IDS) note that it might be difficult to harvest sufficient Sca-1+Lin- bone marrow progenitor cells in humans at megadoses required for overcoming major

transplantation barriers (see abstract). The instant specification also fails to provide any guidance demonstrating that any route of administration of the cardiomyocytes at any site in the treated individual or patient would result in the homing the delivered differentiated second cell population in an effective amount to the heart to yield the desired therapeutic effects contemplated by Applicants. It is also unclear whether the administered cardiomyocytes are capable of establishing the architecture needed to restore or reconstitute cardiac function in the treated individual and/or how long can they survive.

Since the prior art at the effective filing date of the present application does not provide guidance for the issues discussed above, it is incumbent upon the present application to do so. Furthermore, the physiological art is recognized as unpredictable (MPEP 2164.03).

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues discussed above, the unpredictability of the physiological art particularly the art on tolerance induction and/or cardiac repair or regeneration for human allograft patients using cell populations differentiated from human pluripotent stem cells, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to **make and use** the presently claimed invention.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gerald Leffers, Jr., Ph.D., may be reached at (703) 305-6232, or SPE, Remy Yucel, Ph.D., at (703) 305-1998.

Quang Nguyen, Ph.D.

PATENT EXAMINER
Gerald G. Leffers Jr
A.U. 1636